

## EXHIBIT Q

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Inhibition of angiogenesis and metastases of the Lewis-lung cell carcinoma by the quinoline-3-carboxamide, Linomide.

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Linomide has antitumor effects when administered in vivo but not in vitro. Recent data indicate that at least part of this effect can be attributed to anti-angiogenic properties. The aim of the present investigation was to study the anti-angiogenic effects of Linomide on early tumor-induced angiogenesis in vivo, using a newly developed skinfold chamber technique in the mouse, and to relate this to the effect of Linomide on the number of metastases that develop from a s.c. implanted tumor. Tumor spheroids of Lewis lung cell carcinoma (LLC) with a diameter of about 800 microns were implanted in dorsal skinfold chambers inserted on CB6/F1 mice. Tumor cells were pre-labelled with a fluorescent vital dye (CMTMR), which allowed the estimation of the growth of the implanted tumor spheroids. Linomide, given orally from day 7 to day 11, reduced the incidence of lung metastasis arising from LLC tumors at day 21 in a dose-dependent manner, a 55% reduction being found at a dose of 50 mg/kg/day (N = 19 for the controls and N = 10 for treatment groups). In the dorsal skinfold chamber, the vascular network in Linomide treated animals (100 mg/kg/day, N = 22) was more heterogenous, large areas within the tumor being completely avascular; in addition, capillary density at the tumor site was reduced by 34% 6 days after implantation and by 39% after 14 days. In the control group (N = 16), tumor volume doubling time was not significantly different in the early avascular part of the observation period as compared to the later vascular phase; this indicates that the growth of these microtumors in the early avascular phase is not angiogenesis dependent. However, in the Linomide treated animals, tumor volume doubling time was significantly prolonged by 42% during the later part of the observation period. Taken together, the data indicate that the prolongation of the tumor doubling time is due to the anti-angiogenic activity of Linomide.